Remarks

Claims 1, 2, 6-65, and 80-85 are pending in the application. Claims 1, 2, 6-20, 23-25, 27, 28, 30, 37, 46-65, and 80-85 stand rejected, and claims 21, 22, 26, 29, 31-36, and 38-45 have been withdrawn from consideration. Claim 63 is amended as above. No new claims have been added. No new matter is added to the Specification by these changes. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejection under 35 U.S.C. § 112, first paragraph, for lack of written description.

Claims 1, 2, 6-20, 23-25, 27, 28, 30, 37, 46-61, and 80-85 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. The Examiner maintains that the claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states that the amendment to the rejected claims changing the claim language to solid microparticles represents a departure from the specification and the claims as originally filed, and the Examiner has requested that the Applicant point to support in the Specification for such an amendment.

Applicant submits that the claim language "solid microparticles" is supported by the Specification as originally filed. The term "solid" is used to distinguish the microparticles of the invention from liposomes or other particles of a more fluid nature. Applicant submits that support for this use of the term "solid" in the claims can be found in the Specification on page 3, lines 8-11. One of ordinary skill in this art reading the first three sentences of the "Summary of the Invention" would understand that the microparticles of the invention are substantially solid. For instance, the first sentence states that the agent is "encapsulated in a lipid-protein-sugar matrix" implying that the particles are substantially solid. Furthermore, a scanning electron micropgraph of a spray dried lipid-protein particle is shown in Figure 1 indicating that the particles are substantially solid and are not liposomes. Also, support for the term "solid" can be found on page 23, lines 12-15, where various methods of preparing the inventive microparticles

are described. The listed methods including spray drying, single and double emulsion solvent evaporation, and solvent extraction yield substantially solid particles. These methods would not yield a liposome or other more fluid-like particle. Therefore, Applicant submits that one of skill in the art reading the specification and viewing the figures would understand that the particles of the invention are substantially solid and are not liposomes. The amendment to the claims adding the adjective "solid" to further describe the microparticles is adequately supported by the Specification and does not constitute new matter. Applicant requests that the rejection be removed.

II. Rejection under 35 U.S.C. § 102(b), as being anticipated by Moynihan. Claims 63 and 64 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Moynihan (U.S. Patent 5,589,189). Applicant has amended independent claim 63 to recite "solid microparticles." Although Moynihan may teach active agents encapsulated in liposomes, Moynihan does not teach the solid microparticles of the claimed invention. As would be clear to one of skill in the art reading the present application, the claimed invention does not include agents encapsulated in liposomes. In contrast, the claimed microparticles are solid unlike liposomes as described herein. Applicant submits that the amended claims are not anticipated by Moynihan and respectfully requests that the rejection be removed.

III. Rejection under 35 U.S.C. § 102(a), as being anticipated by Bot *et al.* (U.S. Patent 6,423,345). Claims 1, 2, 6, 7, 13, 17-20, 23-25, 27, 28, 30, 37, 46, 48-53, 57-60, 62-65, and 80-85 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Bot *et al.* (WO 00/00215). Applicant submits herewith a Declaration by Dr. Daniel S. Kohane, an inventor of the claimed invention, for the purpose of removing the Bot *et al.* reference from consideration by the Examiner. The Bot *et al.* reference was published as WO 00/00215 on January 6, 2000. Dr. Kohane in his Declaration states that the claimed invention was conceived before January 6, 2000, the filing date of the Bot *et al.* reference, and that the invention was developed with reasonable diligence from the time of conception up until the filing of the provisional application, USSN 60/240,636, filed October 16, 2000, which the present application claims

priority to. As evidence of this fact, Exhibit A of the Declaration is two pages from Dr. Kohane's laboratory notebook describing the preparation and analysis of lipid-protein-sugar particles of the claimed invention.. The notebook pages bear a date before January 6, 2000; however, the dates have been redacted.

In addition, Exhibit B is an early version of a manuscript entitled "Biocompatbility of lipid-protein-sugar particles containing bupivacaine in the perineurium." The work described in the manuscript was incorporated into the present application as Example 1 on page 26 to provide adequate support for the claimed invention. The cover page of the manuscript bears a date prior to the publication date of the Bot *et al.* reference, January 6, 2000; however, the date has been redacted.

In light of the Declaration by Dr. Kohane, Applicant submits that the claimed invention was conceived before the publication of the Bot *et al.* reference and requests that the reference be removed from consideration by the Examiner.

IV. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Moynihan (U.S. Patent 5,589,189). Claims 1, 2, 6, 7, 13, 16, 18-20, 23-25, 27, 28, 30, 37, 46, and 57-61 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Moynihan (U.S. Patent 5,589,189). The Examiner states that although Moynihan does not specifically teach that the liposome formulations are solid, it does teach that the liposomes are suitable for lyophilization. The Examiner proposes that lyophlization would result in solid, dry particles. Applicant disagrees with this suggestion. Even though Moynihan says that the liposome formulation is suitable for lyophilization, there is no evidence that Moynihan did lyophlize his compositions. Furthermore, there is no suggestion or teaching that lyophilizing such a formulation would result in solid, dry particles as the Examiner has speculated. It is not even clear from the vague, one sentence pointed to by the Examiner that Moynihan is removing water from the inside of his liposome particles. Rather it suggests that Moynihan is simply removing water from the solution the liposomes are suspended in. It is likely that lyophilization to the extent suggested by the Examiner would in fact result in destruction of the individual liposomes and would *not* lead to solid, dry particles as the Examiner has suggested. Therefore, since there is no reasonable

expectation that the Examiner's proposed lyophilization would result in the claimed solid microparticles, Applicant submits that the rejection must be removed.

V. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345).** Claims 1, 2, 6, 7, 12-20, 23-25, 27, 28, 30, 37, 46-65, and 80-85 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345). Examiner states that "Bernstein *et al.* teaches that the matrix can be formed of synthetic or natural polymers, including proteins, such as albumin, and polysaccharides (sugars)." However, Bernstein does not teach the claimed combinations to form a matrix of the microparticles. Bernstein *et al.* in fact just teaches the addition of a lipid or other hydrophobic compound to the matrix of microparticles. Although Bernstein *et al.* teaches that the polymeric matrix may be a synthetic polymer, a polysaccharide, or a protein, Bernstein *et al.* does not teach the claimed combinations. The Examiner even admits that "Bernstein *et al.* does not specifically teach a matrix comprising all four of said components."

However, an important aspect of the claimed invention is the recognition that various combinations of proteins, sugars, lipids, and synthetic polymers can be used to formulate microparticles useful in the drug delivery arts. Applicant submits that the Examiner has not established a *prima facie* case of obviousness by merely concluding that the Bernstein *et al.* "patent provides general teachings that synthetic polymer, lipid, protein and sugar can all be used to form the matrix of solid microparticles." Bernstein *et al.* must particularly disclose, teach , or suggest such claimed combination to render the claimed invention obvious. Therefore, Applicant requests that the rejection be removed.

Also, claims 6, 82, and 83 do not include a lipid as an element of the matrix of the inventive microparticles. Bernstein *et al.* clearly teaches a lipid as part of the polymeric matrix (U.S. Patent 6,423,345, col. 1, lines 63-66, and claims). Bernstein *et al.* cannot render obvious the claimed microparticles that do not include a lipid. Therefore, for claims 6, 82, and 83, there is an additional reasons for removal of the Examiner's rejection.

VI. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345) and further in view of Goldenheim *et al.* (U.S. Patent 6,534,081). Claims 8-11 have been rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345), and further in view of Goldenheim *et al.* (U.S. Patent 6,534,081). Although Goldenheim *et al.* may teach the preparation of local anesthetics "in matrices of biodegradable controlled release injectable microspheres," the teachings of Bernstein *et al.* as described above fail to teach the claimed combinations of lipid, protein, sugar, and synthetic polymers in the matrix of the microparticles. Since Goldenheim *et al.* and Bernstein *et al.* even when combined do not teach all the elements of the claimed invention (*i.e.*, combination of materials of matrix), the combined references do not render the claimed invention obvious. Applicant, therefore, requests that the rejection be removed.

VII. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215). Claims 47 and 54-56 have been rejected by the Examiner under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215). As discussed above, the Bot *et al.* reference has been removed from consideration as prior art reference under 35 U.S.C. § 102(a) by the Declaration submitted by Dr. Kohane. Applicant, therefore, requests that this rejection be removed.

VIII. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215) in view of Goldenheim *et al.* (US Patent 6,534,081). Claims 8-11 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215) in view of Goldenheim *et al.* (US Patent 6,534,081). As discussed above, the Bot *et al.* reference has been removed as a prior art under 35 U.S.C. § 102(a) by the Declaration submitted herewith. Without the teachings of Bot *et al.*, the Examiner has not established a *prima facie* case of obviousness; therefore, Applicant requests that the rejection be removed.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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